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## A Review Editorial About Diabetic Nephropathy and Complication Due to Diabetes



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### ABSTRACT

Changes in lifestyle i.e. lethargic and human behavior, result in a dramatic increase in diabetes worldwide, in recent days, diabetic mellitus and its chronic complications are increasing in epidemic proportion. This, unfortunately, results in an increase in pain in the body and damage in body organs like kidneys, liver, out of which kidney is mostly affected and result in diabetic neuropathy. A most chronic complication of diabetes and the most common cause of neuropathy is diabetic neuropathy, which usually results in damage to the kidney. Diabetic neuropathy is common and complication of both in a patient with any type 1 and type 2 diabetes. Diabetic neuropathies are of two types, named sensor motor and autonomic neuropathies. Pain, sensory loss and paraesthesia, are marked by Sensory-motor neuropathy and autonomic neuropathy may result in myocardial infarction, malignant arrhythmia, and sudden death. This article contains a detailed introduction, diagnostic identification, treatment of diabetic neuropathy. Apart from strict glycemic control, there is no specific therapeutic control in the prevention of this phenomenon, because other treatments are not very effective.

## INTRODUCTION:

The International Diabetes Federation approximation that 425 million people worldwide have diabetes<sup>11</sup>, the largest global epidemic of the 21st century<sup>12</sup>, 73 million in India, 115 million people in China and 30 million in the United States has diabetes patients<sup>13</sup>. These numbers are outvalued by the number of individuals with prediabetes, which is estimated to be 388 million in China<sup>14</sup>, 133 million in India<sup>15</sup>, and 85 million in the United States<sup>16</sup>. This number continues to increase at an unsustainable rate.<sup>17</sup>

Diabetic neuropathy is the most common chronic complication of diabetes.

The three major complications of diabetes, diabetic neuropathy is frequent and appears earliest after the onset of diabetes.

It has various clinical symptoms from head to toe and is caused by damage to the peripheral and autonomic nervous system, generally referred to as different forms of neuropathy, these syndromes are caused by diffuse and focal nervous system damage and occur in up to half of all individuals with diabetes.<sup>18</sup>

Identification of early signs of neuropathy in Diabetic patients, early diagnosis, and appropriate management in the early stages is very important for the following reason.

- First, diagnosis of diabetic neuropathy is difficult because multiple tests are required examination methods are complicated and time-consuming.
- Second treatment for symptomatic diabetic neuropathy is available.
- Third diabetic neuropathy can be asymptomatic in up to 50% of cases.

Asymptomatic diabetic neuropathy is a sign of serious complications.

The most common form of diabetic neuropathy is distal symmetric polyneuropathy. Distal symmetric polyneuropathy manifests with a 'stocking and glove' distribution, whereby the hands and lower limbs and slowly spread proximally.<sup>19</sup>

It was only in 1864 that diabetes mellitus was recognized as a cause of peripheral neuropathy.

Some year later the involvement of cranial nerve of diabetic patients has been observed.<sup>20</sup>

- The loss of tendinous reflexes in the lower limb was described by BOUCHARD in 1884.<sup>21</sup>
- The presence of spontaneous symptoms such as a pen and hyperesthesia was described by PAVY in 1885.<sup>22</sup>
- The first classification was suggested by LEYDEN IN 1893.WHO subdivided into sensory and motor manifestation.<sup>23</sup>
- **JORDAN AND CRABTREE** [1935] in intern were the first mention pathophysiologic diabetic neuropathy mechanism.<sup>24</sup>
- Studies by **FAGERBERG**,<sup>25</sup>**MULDER ET AL.**<sup>26</sup> **AND PIRAT, LASUVAUX AND REY**,<sup>27</sup> have been proven the correlation of diabetic neuropathy with other microvascular complications such as diabetic neuropathy and retinopathy.<sup>28</sup>

Diabetic neuropathy (DN) is a common disorder and is defined as signs and symptoms of peripheral nerve dysfunction in a patient with diabetes mellitus (DM). There is a higher universality of DM in India (4.3%)<sup>29</sup> as compared to the West (1%–2%).<sup>30</sup>

Mostly in Asian Indians are more prone to insulin resistance and cardiovascular mortality.<sup>31</sup>The incidence of DN in India is not well known but in a study from South India 19.1% of type II diabetic patients had peripheral neuropathy.<sup>32</sup>

Diabetes has become one of the largest global health issues of the 21<sup>st</sup> century. There are numbers of people who suffer a diabetes problem worldwide is speculate to double between 2000 and 2030, reaching a pandemic level of 366 million people. <sup>33</sup>

#### **CLASSIFICATION:**

Diabetic neuropathy is of 2 types that include diffuse and focal.

**Table No. 1 Classification of diabetic neuropathy:**

<b>TYPE OF NEUROPATHY</b>	<b>CLASSIFICATION</b>	<b>EXAMPLES</b>
<b>Diffuse</b>	symmetric polyneuropathy diffuse sensory- motor	small-fiber long-fiber mixed
	autonomic neuropathy	abnormal pupillary function sudomotor dysfunction genitourinary gastrointestinal cardiovascular maladaptive to hypoglycemia
<b>Focal</b>		Mononeuropathy Multiple Mononeuropathy Plexopathy Radiculopathy Cranial Neuropathy

**Classification of diabetic neuropathy:**

A. Diffuse

1. Symmetric Polyneuropathy diffuse sensory-motor

2. Autonomic neuropathy

a. Sudomotor

b. Cardiovascular

c. Gastrointestinal

d. Genitourinary

3. Symmetric proximal lower limb motor neuropathy (amyotrophy)

## B. Focal or Mononeuropathies

1. Cranial neuropathy
2. Radiculopathy/plexopathy
3. Entrapment neuropathy
4. Asymmetric lower limb motor neuropathy

## A. DIFFUSE DIABETIC NEUROPATHY

### 1. Symmetric polyneuropathy diffuse sensory-motor:

- This is the most common type of diabetic neuropathy which includes all small, large, and mixed fibers.
- Firstly most distal parts are affected, which mostly result in loss of sensory stocking pattern.<sup>2</sup>
- These are the series of sensory loss that is-

Knees → distal upper limbs → anterior aspect of trunk → finally the involvement of vertex of the head

- It is mostly sensory neuropathy, motor defect occur in rare cases
- Symptoms of this range from extremely painful to painless. Also, neuropathic symptoms are positive or negative:

Positive symptoms are- burning pain, altered and uncomfortable temperature perception, paraesthesia, shooting, stabbing, and lancinating pain.

Negative symptoms are- numbness and deadness in the lower limbs.

- Foot deformity mostly occurs in motor symptoms. This abnormality occurs redistributes weight-bearing and leads to callus and ulcer formation.

### 2. Autonomic neuropathy

A very serious form of diabetic neuropathy, the autonomic nerve that is present at any part of the body can be affected. Studies have confirmed the presence of parasympathetic dysfunction in 65% of type 2 diabetic patients 10 years after diagnosis and of combined

parasympathetic and sympathetic neuropathy in 15.2%<sup>1</sup>. Among autonomic neuropathic symptoms, gustatory sweating is most common, followed by postural hypotension and diarrhoea<sup>3</sup>. This may range from minor to severe and also several forms may affect survival and may result in death.

Signs and symptoms of autonomic neuropathy<sup>4</sup>

- Cardiovascular
  - Postural hypotension
  - Resting tachycardia
  - Painless myocardial infarction
  - Sudden death (with or without association with general anesthesia)
- Gastrointestinal
  - Oesophageal motor incoordination
  - Gastric dysrhythmia, hypomotility (gastroparesis diabeticorum)
  - Pylorospasm
  - Uncoordinated intestinal motility (diabetic diarrhoea, spasm)
  - Intestinal hypomotility (constipation)
  - Gallbladder hypo contraction (diabetic cholecystography)
- Genitourinary
  - Diabetic cystopathy (impaired bladder sensation, atonic bladder, post micturition dribbling, detrusor hyporeflexia, or hyperreflexia)
  - Male impotence
  - Ejaculatory disorders
  - Reduced vaginal lubrication, dyspareunia
- Pupillary
  - Miosis

➤ Disturbances of dilatation

➤ Argyll Robertson pupil

### 3. Symmetric proximal lower limb motor neuropathy (amyotrophy)

It affects both male and females, but in male, it affects at elder age i.e. above 50 years suffering from type 2 diabetes and in a female with type-1 diabetes. The patient usually presents with difficulty in getting up from a squatting position, pain in climbing stairs, and marked weight loss (sometimes up to 40% of original weight). Sometimes, other muscles, especially the anterior tibial and peroneal muscles may also be involved<sup>5</sup>. From sensory loss or not to symmetrical or asymmetrical, it can be of any type. Anterior and adductor compartments of the thigh are predominantly affected. This has been labeled as diabetic amyotrophy also.

## B. FOCAL OR MONONEUROPATHIES

Most of the diabetic patients are suspected to get focal neuropathies:

### 1. Cranial neuropathy:

Cranial nerves are mostly involved in this type and mostly occur in the stage of the elderly. That cranial nerve that gets involved is Third, fourth, and sixth.<sup>6</sup> Eye pain, diplopia, and ptosis are due to the third cranial nerve but there is usually spared in pupillary response. Within 6-12 weeks, spontaneous recovery occurs, but there may be chances of recurrent and bilateral lesions.<sup>7</sup>

### 2. Truncal neuropathy:

This is a less common type of neuropathy (symptomatic truncal polyneuropathy), but long-standing diabetes with other microvascular complications may occur, with gradual onset of pain, it usually presents and dysaesthesia in the lower anterior chest or upper abdomen with nocturnal intensification. Hypoesthesia or hyperaesthesia may present on examination in appropriate thoracic segment abdominal swelling due to abdominal muscle weakness.

### 3. Entrapment neuropathy:

As the name suggests, it restricts the mobility of the patient. Also known as PRESSURE PALSY and it is an uncommon type. The ulnar or lateral cutaneous nerve of the thigh may

get affected. The median nerve is mostly affected and is secondary to soft tissue changes associated with limited joint mobility.

### **PATHOGENESIS:**

Diabetic peripheral neuropathy encompasses sensory, motor, and autonomic neuropathy. There are many hypotheses for the pathogenesis of diabetic neuropathy. Implicated causes of peripheral nerve damage include oxidative stress damage, accumulation of sorbitol and advanced glycosylation end products as well as a disturbance of hexosamine, protein kinase C, and polymerase pathways.

Chronic neuropathy is mostly due to persistent hyperglycemia while acute, usually self-limiting neuropathy may be due to vascular causes.

Hyperglycemia results in accumulation of advanced glycosylated end products and activation of some pathways that result in oxidative stress, axonal loss, and demyelination due to which, nerve dysfunction occur.<sup>51</sup>

Sometimes, excess glucose, that present in our body gets converted to sorbitol by the enzyme aldose reductase. Sorbitol which is formed decreases the level of myoinositol nerve growth factor which leads to diabetic neuropathy.

So, controlling glucose to an optimal level is a primary preventive measure.



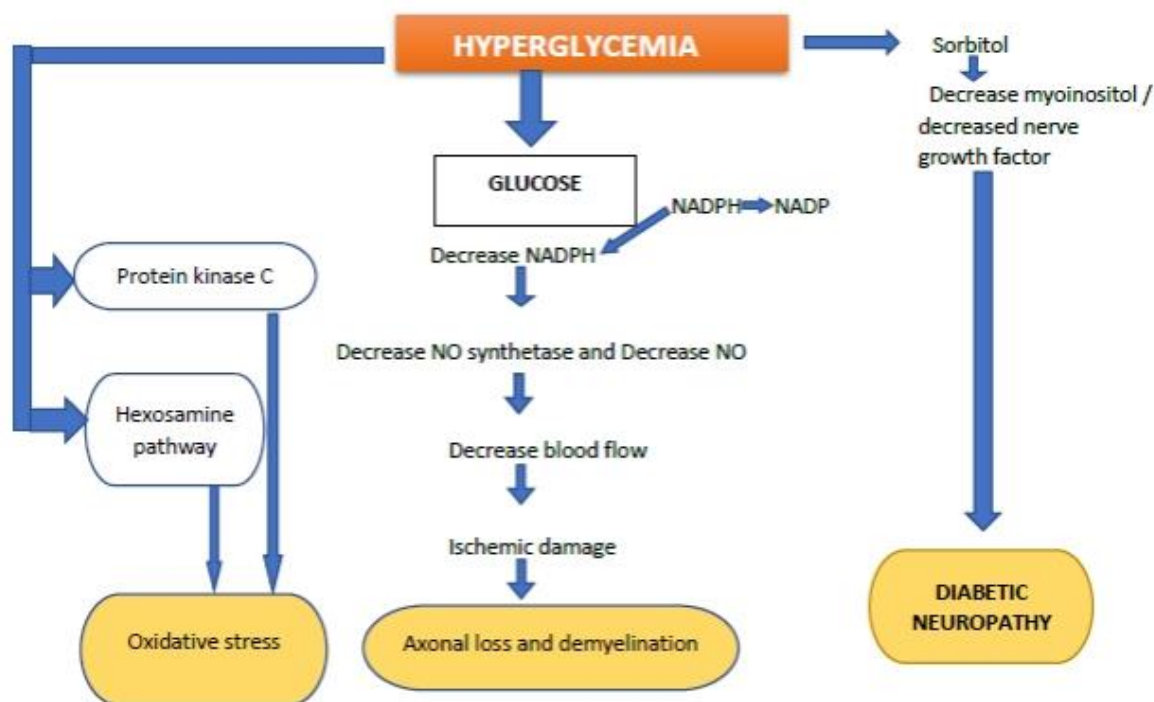


Figure No. 1: pathogenesis of diabetic neuropathy

## DIAGNOSIS:

Your doctor will do a physical exam and ask about your symptoms. To diagnose DN, it include various evaluations of muscle power, sensations of a pinprick, joint position, touch, and temperature. A vibration test should be done by tuning fork of a 128 Hz. For touch sensation monofilament of 1 g is recommended. The sensory examination should be performed on hands and feet bilaterally<sup>34</sup>, you should be checked once a year for DPN if you have any foot problems. The doctor will check for loss of feeling in your feet by seeing whether you can feel light touch, pinpricks, and vibrations from a tuning fork. Your doctor will also make sure you don't have other conditions, such as blood flow problems or a vitamin deficiency.

The autonomic function tests commonly used in DM are based on blood pressure and heart rate. The doctor recommends Specific tests are used for evaluating gastrointestinal, genitourinary, ultrasound, breathing test, and peripheral skin blood flow.

**Breathing tests-** These tests measure how your heart rate and blood pressure respond during exercises such as forcefully exhaling.

**Gastrointestinal tests-** Gastric-emptying tests are the most common tests to check for digestive abnormalities such as slow digestion and delayed emptying of the stomach. These tests are usually done by a doctor who specializes in the digestive disorder.

### **Diagnostic Tests of Autonomic Neuropathy**

#### ➤ **RESTING HEART RATE**

>100bpm is abnormal.

#### **Beat –To – Beat Hrv**

- At rest and supine heart rate by ECG while the patient breathes at 6/m.
- Difference of >15 bpm –normal, <10 bpm –abnormal.
- The lowest normal value for the expiration-to-inspiration ratio of the R-R interval is 1.17 in 20-24 years of age.

#### **Heart Rate Response to Standing**

- R-R interval measured at beats 15 and 30 after standing.
- Normally, tachy F.B reflex Brady. The 30:15 ratio is 1.03.

Nerve biopsy may be useful for excluding other causes of neuropathy<sup>35</sup>. Confocal microscopy, the cornea is scanned and the images of Bowman's layer, which contains a rich nerve plexus, are examined for nerve fiber density, length, and branch density. Confocal microscopy may have great potential in appraise nerve structure in vivo without the need for nerve biopsy.<sup>36</sup>

The American Academy of Neurology recommends that DN is diagnosed in presence of somatic or autonomic neuropathy when another problem of neuropathy has been included.

DN may be asymptomatic in several patients. The five criteria are needed to examine the DN which exclude symptoms, signs, electrodiagnostic tests, quantitative sensory, and autonomic testing.<sup>37</sup>

The unanimity regarding the diagnosis of DPN has changed since 2004. The AAN recommends an NCV with both neuropathic symptoms and signs as confirmation of DPN<sup>38</sup>. The European Federation of Neurological Societies proposed a skin biopsy and

intraepidermal nerve fiber density as sensitive measures to diagnose small nerve neuropathy.

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## PREVENTION

- There is a lack of treatments of DN. Therefore, the prevention of DPN is a key component of diabetes care.<sup>40</sup>
- Prevention of DN is depending on glycemic control and your lifestyle.
- Treatment of hyperglycemia logically would be the best preventive treatment for diabetic neuropathy.
- Lifestyle is also being preventive DPN.
- neuropathy. Impact of glycaemic control strategies in the progression of DN.

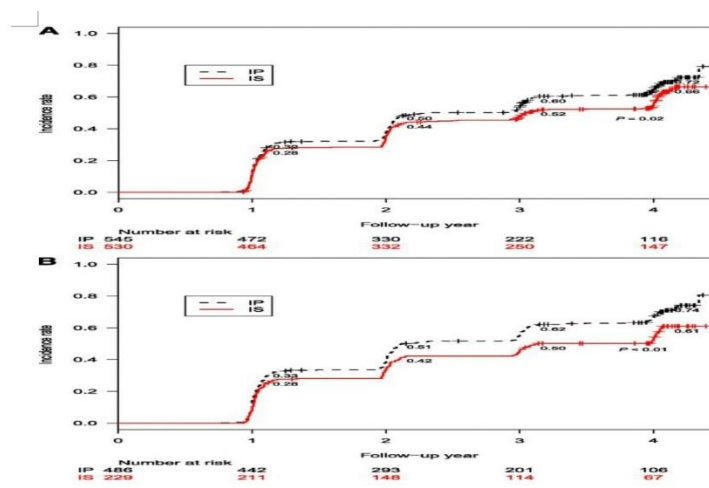


Figure No. 2: Graphical representation

- Optimize glucose control as early as possible to prevent or delay the development of distal symmetric polyneuropathy and cardiovascular autonomic neuropathy in people with type 1 diabetes.
- Enhance glucose control to prevent or slow the progression of distal symmetric polyneuropathy in people with type 2 diabetes.
- The American Diabetes Association recommend achieving optimal glucose control in type 1 and type 2 diabetes to prevent or slow the progression of DPN.<sup>42</sup>
- Glycemic control may result in a 60 percent demotion in the risk of developing clinical

- Patients having diabetes also need to foot care and footwear.
- Exercise is also a promised that exercise is a good preventive strategy in diabetic neuropathy. <sup>44</sup>
- The study indicates that exercise having the potential to prevent nerve injury and even promote nerve regeneration, while the study was not randomized and the effect on patient-oriented neuropathy outcomes is still not clear But the exercise recommended the patient who has diabetes based on daily routine. <sup>45</sup>
- In a small trial of Japanese patients with early type 2 diabetes, thoroughgoing on insulin treatment was associated with improvement in selected DSPN measures<sup>46</sup>, and the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial reported a modest but significant DSPN risk reduction with the glycemia intervention in individuals with type 2 diabetes after 5 years of follow-up. <sup>47</sup>
- Only one study has focused on neuropathy outcomes after bariatric surgery, although this study did not focus on prevention. This prospective cohort study demonstrated significant improvements in neuropathy outcome measures 6 months after Roux-en-Y gastric bypass surgery in patients with T2DM and preoperative diabetic neuropathy. <sup>48</sup>

## MANAGEMENT

There is no specific treatment for diabetic neuropathy. It can only be managed or prevented by specific methods.

General treatments of diabetic neuropathy are:

1. Glycaemic control
2. Pain control
3. Foot care<sup>9</sup>

### 1. GLYCAEMIC CONTROL:

- Tight glycaemic control is the only technique that has been demonstrated to show the prevention of diabetic peripheral and autonomic neuropathy. It can be prevented or avoided by managing your blood glucose vigilantly.

- Glucose control was associated with improved vibratory sensation in UK prospective diabetic studies.<sup>10</sup>
- Bp control, dyslipidemia control, also involved in treatment with lifestyle modifications exercise, and cessation of smoking and alcohol.

## 2. PAIN CONTROL:

Some medications are available in table no 2.

- Symptomatic treatment of painful neuropathy:

The quality of life of an individual is significantly improved by optimal management and pain and paresthesia are distressing symptoms of painful neuropathy. As symptomatic diabetic neuropathy a type of neuropathy that causes pain, so pain sometimes may be very severe to intolerable. So it requires agents to solve this, Some degree of comfort is provided by some options available for symptomatic treatment of paresthesia and dysesthesia as described below:

*For symptomatic treatment of diabetic neuropathy, some available agents are:*

Some agents for symptomatic treatment of neuropathy are in table 1<sup>49</sup>.

❖ Tricyclic antidepressants: Most powerful and most cost-effective therapy of diabetic neuropathy is this. Dose differs from low dose to high dose i.e in doses of 25 mg and increased by increments of 25 mg usually up to 150 mg. Desipramine, Nortriptyline which is norepinephrine reuptake inhibitors, are also beneficial for its management.

Caution

- Cardiac arrhythmia may worsen, so it is recommended to check electrocardiogram.
- Prostatic hypertrophy can be worsening. **Erectile dysfunction, Anticholinergic effects may limit their usage.**
- ❖ Anticonvulsants: to relieve the pain of neuropathy, Anticonvulsants have a major role, if used in optimal doses. But in hyperglycemia, some drugs should be avoided like sodium phenytoin.
- Carbamazepine: In symptomatic treatment of paresthesia, it is most commonly used. It rarely causes Stevens-Johnson syndrome. In higher dose, it can cause ataxia.

- Gabapentin: In chronic pain, gabapentin help patients to show improved sleep.
- Pregabalin: As it is superior to gabapentin, it is more used.

Pregabalin and gabapentin have same mechanism of action i.e they decrease calcium influx at nerve terminals modulating neurotransmitter release by binding to subunit voltage-sensitive calcium channel.

*Adverse effects:* Dizziness, somnolence, and peripheral edema.

Opioids are also used in addition in the treatment of symptomatic painful neuropathy, besides analgesics Non- Steroidal anti-inflammatory drugs (NSAIDS).

**Table No. 2: Medications used to treat symptomatic diabetic neuropathy (modified from Canadian diabetic Association guidelines)**

CLASS	EXAMPLES	STARTING DOSE	MAXIMUM DOSE OF NEUROPATHY
<b>Tricyclic Drugs</b>	Amitriptyline Nortriptyline Imipramine	10mg At Bedtime 25-75mg At Bd 25-75mg At Bd	150mg/Day
<b>Anticonvulsants</b>	Gabapentin Carbamazepine Pregabalin	300mg Bd 200mg Tid 75mg Od	900mg/Day 800mg/Day 200mg/Day
<b>5-Ht And Norepinephrine Reuptake Inhibitor</b>	Duloxetine	60-120mg Od	120mg/Day
<b>Substance P Inhibitor</b>	Capsaicin Cream	0.025-0.075% Preparation For Local Application	5-6 Applications/Day
<b>Antipyretics Semisynthetic Opioids</b>	Paracetamol Tramadol	500mg 50-100mg	2500mg/Day 400mg
<b>5-Ht: 5-Hydroxytryptamine</b>			

- Deep-seated pain: (treatment options)

Some individuals with diabetic neuropathy, experience deep-seated or poorly localized pain. The following option may be used in the management of this type of pain:

- Opioid analgesics: It is the most effective semi-synthetic opioid tramadol and it is less addictive than other opioid derivatives and in combination with acetaminophen it is effective in curbing deep pain.
- Transcutaneous electrical nerve stimulation: In deep-seated pain, it is effective in its therapy.
- Local application of capsaicin ointment: It is useful in adjuvant therapy in randomized trials.

### **Other Medications Used For Diabetic Neuropathy:**

There are several other medications which are used in diabetic neuropathy with different level of pathogenesis. Many of the agents used below are new and used in different phases of a clinical trial.

- Alpha-lipoic acid
- Ruboxistaurin
- Recombinant nerve growth factor
- Topical nitric oxide
- Aldose reductase inhibitors
- High myoinositol diets

### **3 Foot Care:**

Foot care and the use of appropriate footwear are very important for the care of diabetes. People with foot deformities, if wear tight or ill-fitting footwear, can result in abnormal pressure over bony prominences. This pressure leads to blister formation and skin breakdown over time due to loss of sensation. Foot ulcers cause due to fissure and callus which may lead to physical disability, so this must be prevented. Educating the patient for the care of foot during diabetes neuropathy is very vital for the patient.

Table No. 3: Foot care prescription

<b>Foot care prescription for diabetic patients with lower extremity sensory neuropathy<sup>50</sup></b>
• <b>Never walk barefoot</b>
• <b>Do not apply hot water or heating pads to the feet</b>
• <b>Inspect the feet daily, using a mirror for plantar surfaces</b>
• <b>Wash the feet daily, drying thoroughly between the toes</b>
• <b>Lubricate dry skin to avoid cracking</b>
• <b>Wear clean, soft, cotton socks</b>
• <b>Wear properly fitting, well-cushioned shoes [insoles]</b>
• <b>Break-in new shoes slowly</b>
• <b>Consider a second pair of shoes at night [larger size for dependent edema]</b>
• <b>Cut toenails straight across, to conservative lengths</b>
• <b>Schedule regular visit to a diabetic foot care</b>

**Foot care and footwear:**

“Foot problems can be prevented by Simple foot care and Proper footwear”.

Ulcers, sores, are very common problems during diabetic neuropathy. You can control it by:

- Check your feet every day
- Keep your feet clean and dry
- Moisturize your feet
- Trim your toenails carefully
- Wear clean and dry socks
- To prevent cracking and drying, the cream may be applied
- Nails should be cut transversely
- Avoid exposure to heat



**Foot care in large fiber neuropathy:**

**GAINT STRENGTH TRAINING:** due to coordination weakness, muscle wasting, patient with large fiber neuropathy have an increased predisposition to falls. By high-intensity strength training, coordination, and balance training help to reduce falls and resultant fractures and also improving muscle strength. Advise use of MCR footwear.

**Callus and fissure care:**

Development of fissure: *Dysautonomia*

Autonomic neuropathy



Dry feet



Fissuring



Infection



Abscess



Ulcer



**Figure No. 3: fissure development:**

Development of callus: *Motorneuropathy*:

Motor neuropathy



Deformity



Abnormal pressures



Callus



Callus hematoma



**Figure No. 4: Callus development**

Abscess/Ulcer

- To callus, apply 6% salicylic acid.
- Soak the foot for 10 min to soften the callus, after a shower or bath.
- Over callus, rub pumice stone. (in one direction)
- Examine footwear and make changes if necessary to look at the cause of callus.

**Toenail care**

- For thick toenails: file the nail down with an emery board.
- Before cutting the nail, soak the feet 10 minutes before to make it soften.
- Trim the nail across, then file the corners.

**CONCLUSION:**

By expressing the overview briefly, we would like to present the current state of diabetic neuropathy. As there are no testing and diagnostic methods have been established, diabetic

neuropathy is not taken into daily clinical practice. In future, it is important to establish a quantitative and simple method of testing to detect asymptomatic diabetic neuropathy and enable aggressive treatment.

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